

SUBSTITUTE FORM PTO-1390

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER
06275-228001

U.S. APPLICATION NO. (If Known, see 37 CFR 1.5)

09/763308

INTERNATIONAL APPLICATION NO.
PCT/SE00/01592INTERNATIONAL FILING DATE
21 August 2000PRIORITY DATE CLAIMED
24 August 1999TITLE OF INVENTION
CHEMICAL COMPOUNDS

APPLICANT(S) FOR DO/EO/US

Per-Ola Arvidsson, Mark Divers and Silja Petersen-Mahrt

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. ☐ The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☒ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ An English language translation of amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern other documents or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

☐
☐
☐
☐
☐

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. **EL624270834US**

I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

2/20/01
Date of DepositDaniel C Messier
SignatureDaniel C
Messier
Typed Name of
Person Signing

U.S. APPLICATION NO. (IF KNOWN) 09/763308		INTERNATIONAL APPLICATION NO. PCT/SE00/01592		ATTORNEY'S DOCKET NUMBER 06275-228001	
17. <input checked="" type="checkbox"/> The following fees are submitted: Basic National Fee (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1000 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... \$710 International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)..... \$690 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)..... \$100 <div style="text-align: right;">ENTER APPROPRIATE BASIC FEE AMOUNT =</div>				CALCULATIONS PTO USE ONLY	
Surcharge of \$130 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$0.00	
Claims	Number Filed	Number Extra	Rate		
Total Claims	14 - 20 =	0	x \$18	\$0.00	
Independent Claims	1 - 3 =	0	x \$80	\$0.00	
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)			+ \$270	\$0.00	
TOTAL OF ABOVE CALCULATIONS =				\$1,000.00	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				\$0.00	
SUBTOTAL =				\$1,000.00	
Processing fee of \$130 for furnishing the English Translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f))				\$0.00	
TOTAL NATIONAL FEE =				\$1,000.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$40.00	
TOTAL FEES ENCLOSED =				\$1,040.00	
				Amount to be refunded:	\$
				Charged:	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$1,040.00 to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. 06-1050 in the amount of \$0.00 to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1050. A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO:					
Janis K. Fraser, Ph.D., J.D. FISH & RICHARDSON P.C. 225 Franklin Street Boston, MA 02110-2804 (617) 542-5070 phone (617) 542-8906 facsimile			<div style="text-align: right; margin-bottom: 10px;"> <i>Willia E Book 28,933</i> SIGNATURE: </div> <div style="text-align: right; margin-bottom: 10px;"> Janis K. Fraser, Ph.D., J.D. NAME </div> <div style="text-align: right;"> 34,819 REGISTRATION NUMBER </div>		

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Per-Ola Arvidsson et al.
Serial No. :
Filed : Herewith
Title : CHEMICAL COMPOUNDS

Art Unit : Unknown
Examiner : Unknown

Box PCT

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the Specification:

On page 4, lines 18-19, delete "2-hydroxypropyl-b-CD" and insert
--2-hydroxypropyl- β -CD--.

On page 6, table of Abbreviations, line 3, column 2, delete "2-hydroxypropyl-b-cyclodextrin" and insert --2-hydroxypropyl- β -cyclodextrin--.

In the Claims:

In claim 4, line 1, delete "any preceding claim" and insert --to claim 1,--.

In claim 6, line 1, delete "any preceding claim" and insert --claim 1--.

In claim 7, line 1, delete "any preceding claim" and insert --claim 1--.

In claim 8, line 1, delete "any preceding claim" and insert --claim 1--.

In claim 9, line 1, delete "any preceding claim" and insert --claim 1--.

In claim 10, line 1, delete "any preceding claim" and insert --claim 1--.

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EL624270834US

I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

2/20/01
Date of Deposit

Daniel C. Messier
Signature

Daniel C. Messier
Typed or Printed Name of Person Signing Certificate

Applicant : Per-Ola Arvidsson et al.
Serial No. :
Filed : Herewith
Page : 2

Attorney's Docket No.: 06275-228001

In claim 10, lines 1-2, delete "2-hydroxypropyl-b-cyclodextrin" and insert
--2-hydroxypropyl- β -cyclodextrin--.

In claim 11, line 1, delete "any preceding claim" and insert --claim 1--.

In claim 12, line 1, delete "any of claims 1-11" and insert --claim 1--.

In claim 13, line 1, delete "any of claims 1-11" and insert --claim 1--.

REMARKS

Claims 1-14 are now pending. The amendments to the pending claims delete multiple dependency. No new matter has been added.

Applicants submit that all of the claims are now in condition for examination, which action is requested. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: _____

Feb 20, 2001

William R Booth 29933

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

09/763308

Attorney's Docket No.: 06275-228001

JC02 Rec'd PCT/PTO 20 FEB 2001

APPLICATION
FOR
UNITED STATES LETTERS PATENT

TITLE: CHEMICAL COMPOUNDS

APPLICANT: PER-OLA ARVIDSSON, MARK DIVERS AND
SILJA PETERSEN-MAHRT

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EL624270834US

I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

2/20/01
Date of Deposit

Daniel C Messier
Signature

Daniel C Messier
Typed or Printed Name of Person Signing Certificate

CHEMICAL COMPOUNDS

The invention relates to cyclodextrin as a protective agent for compounds in compound libraries, particularly for use in screening the compound library for biological activity.

5 High Throughput Screening (HTS) is a process in which up to many thousands or more of chemical compounds are assayed in search of biological (or other) activity. Large libraries of chemical compounds are valuable assets of research organisations. Compound libraries are used in the search for agents with novel pharmaceutical, agrochemical or other fine chemical applications and are a valuable source of structural and chemical diversity used
10 in identifying new leads as potential inhibitors of a particular target. Compound libraries may for example contain more than 100,000 different compounds and due to increasingly efficient compound acquisition, either through commercial sources, or by high throughput synthesis, compound libraries with more than 1 million different compounds are now of a typical size in some research organisations. There is a vast variety of targets, and an even greater variety of
15 assay methods. The goal of HTS is to identify "actives", compounds that affect the target in some manner. There are a number of problems set out below which presently hinder the optimal operation of HTS.

The compounds available for testing are called the compound library. The compounds may be hydrophilic, lipophilic, reactive or light-sensitive. The compounds are stored in
20 solution, usually DMSO or a mixture of DMSO and water, to be available for screening. The storage is long-term (e.g. up to 5 years) and the environmental conditions are very variable. Because of the large variety of properties in the compound library, the conditions for storage can not be adjusted to individual compounds and compromises are made to suit most of the compounds and the screening process. For the screening process, the individual compounds
25 are transferred to reaction vessels (e.g. microtitre plates) in small (e.g. sub-microliter) quantities. For performing a biological assay, the compounds are diluted in aqueous solution while adding the biological material, for example enzymes, cells or membranes. A signal is measured, representing the individual biological activity of the compound on that particular target, usually relative to a control (e.g. the biological reaction without compounds).

30 Compromising on storage conditions and the choice of suitable solvent may disqualify many compounds even before they reach the biological assay system. Furthermore, even more compounds may never reach the biological target, because the addition of aqueous solution

causes precipitation of molecules. There is currently no solution to this problem. Progress in screening technology i.e. moving into much smaller assay-volumes reveals another problem. Pipetting of sub-microliter quantities of chemical compounds is now possible, but it is very hard to keep the compounds solubilized, because the solvent rapidly evaporates. Most

5 compounds are not easily resolubilized in aqueous solution once the organic solvent has evaporated and consequently the compound is not available to the biological target. The compromise of diluting in aqueous solution prior to the assay leaves one with the problem of precipitation.

High throughput multiple parallel synthesis (HTMPS) can generate very large
10 numbers of individual compounds, typically 100-5000 per week, but the sample size is usually small, <100mg. Compounds from HTMPS are stored sometimes as dry films or as solutions, usually in dimethyl sulphoxide (DMSO). The dispensing of compounds stored as dry films is often very difficult, and the difficulty increases significantly as the sample size decreases. Compounds stored as solutions can be dispensed quickly and accurately, but some
15 samples are unstable in solution and decompose on prolonged storage, even at low temperatures.

Increasingly the demands of a compound collection are changing. With the advent of high throughput screening (HTS) a whole compound collection of, for example, 100,000 compounds may be screened in a number of days against a new biological target, using
20 automated or semi-automated procedures. Faced with the need for more rapid dispensing of compounds from the compound collection, the small sample size needed and the large numbers of different sample types existing in a compound collection, current systems of storage and dispensing are increasingly incompatible with modern needs.

Much of the developing new technology in drug discovery is focussing on
25 miniaturisation. Along with many big advantages offered by miniaturisation technologies, come the problems of compounds drying out of solution (due to the evaporation of sub-microlitre volumes of solvent) and exposure of compound solutions to aqueous conditions before the screening (which can lead to precipitation of the compounds out of solution).

These problems could prevent the screening of many compound classes, and therefore restrict
30 the benefit of HTS in discovering compounds with useful biological activity.

After the priority date of the present invention, a European patent application from Evotec BioSystems GmbH published on 6Oct1999 as EP 947820. This Evotec publication includes use of cyclodextrins as additives for compound storage.

The present invention is based on the discovery that cyclodextrins can be used as a
5 universal additive to compounds in a compound library to overcome at least some of the problems set out above.

According to one aspect of the present invention there is provided a compound library wherein each compound within the library is stored in the presence of a cyclodextrin. The number of compounds in a compound library which may be stored by the techniques as
10 described herein is not limited by the invention, ideally the invention may be used for storage of compounds in compound libraries where the number of different compounds stored is more than 100, preferably more than 300, preferably more than 10^3 , preferably more than 3000, preferably more than 10^4 , preferably more than 30000, preferably more than 10^4 , preferably more than 10^5 , especially more than 10^6 . Addition of compounds to the library that do not
15 contain cyclodextrin is intended to be within the scope of the present invention provided the library sizes set out above are met with compounds that do contain cyclodextrin.

Preferred compounds are those stored in compound libraries of pharmaceutical, biotechnology or agrochemical companies. Preferred compounds are organic molecules of molecular weight of less than 2000 Daltons, and especially of 1000 Daltons or less.

20 Preferably the compounds within the library are selected from at least 3 chemical classes, more preferably at least 5 chemical classes, more preferably at least 7 chemical classes, more preferably at least 10 chemical classes, more preferably at least 30 chemical classes and especially at least 100 chemical classes. Examples of chemical classes include: acidic, basic and neutral compounds; aliphatic, aromatic and heteroaromatic compounds;
25 carboxylic acids, sulphonic acids, esters, acid halides, amides, amidines, nitriles, aldehydes, ketones, alcohols, phenols, thiols, hydroperoxides, amines, imines, ethers, sulphides and peroxides; and any suitable combination or combinations thereof.

Preferably the cyclodextrin is present at a substantially uniform concentration across the library. A preferred concentration of cyclodextrin is 20-200mM, more preferably at 30-
30 150mM, more preferably at 40-80mM and especially at 45-60mM, and especially at about 50 mM. It will be appreciated that these concentrations refer to the initial concentration upon preparation of a compound for addition to the library and that, over time, the concentration

may increase due to evaporation. It will also be appreciated that for this reason, even when one concentration of cyclodextrin is selected initially, there may be variable concentrations present in the compound library depending on differences in storage time (and therefore extent of evaporation) for individual compounds. Compounds may be purposefully dried before storage or alternatively stored in wet form and natural evaporation (if any) allowed to occur on storage. The Evotec publication states that the compounds must be stored dry (see para 18 of Evotec and the claims).

For the sake of comparison with Evotec, the reader is referred to the following parts thereof which state certain additive concentrations.

para 24: hydroxypropyl- β -CD concentrations of 0.05-4% by weight, 0.05-2% and 0.1-1.5%

Example 1: hydroxypropyl- β -CD concentration of 1.5%.

Example 2: hydroxypropyl- β -CD concentration of 0.1%.

A comparison of concentration units is presented below.

hydroxypropyl- β -CD concentration (mM)	hydroxypropyl- β -CD concentration (% by weight)
20-200	2.8-28
30-150	4.2-21
40-80	5.6-11.2
45-60	6.3-8.4
50	7

15

Therefore the stated additive concentrations herein are novel over Evotec.

One cyclodextrin or a mixture of cyclodextrins may be used, either within a single compound or across the library as a whole. An especially preferred cyclodextrin is 2-hydroxypropyl- β -CD.

According to another aspect of the present invention there is provided a method of preparing a compound library of the invention which comprises the addition of a cyclodextrin to each compound within the library. In one embodiment, the library may be stored in wet form.

According to another aspect of the present invention there is provided a method of screening a compound library of the invention which comprises assay of at least 100

25

compounds from the library in the presence of a cyclodextrin. Preferred assays include enzyme, receptor and cellular models.

The addition of CDs to compound libraries solves at least some of the problems faced with known compound libraries as described above. For example, we have discovered that
5 many structurally different compounds within a compound library are protected against degradation and oxidation in the presence of CDs and they can be widely used to enhance solubility of molecules in aqueous solution. Furthermore compounds can be dried in the reaction vessel without losing their biological activity. CD has not yet shown any effects on the biological systems tested: no inhibition or activation due to the CDs could be shown, and
10 no side-effects on signal-detection have been observed so far. Furthermore, CD has not yet shown any negative effects on compound availability in any tested bioassay.

Without wishing to be bound by theoretical considerations, we believe that some of advantages of the invention may be due, at least in part, to the following properties of CDs. CDs are capable of forming inclusion complexes with drug molecules by taking up the
15 molecules in their cavity. The inclusion complex is in equilibrium with the surrounding environment of water molecules, CD-molecules and free drug molecules. The compounds are readily released from the inclusion complex by dilution in aqueous solution, i.e displacing the equilibrium in favour of the free molecules. Formation and dissociation of the inclusion-complex is a rapid process, usually only minutes. For very hydrophobic compounds the
20 equilibrium is first reached after hours or days. CDs are not only used to enhance solubility but also to stabilize compounds both in dry formulations and in solutions. CDs can prevent compounds from hydrolysis, oxidation and also photodestruction by protecting them from a potentially reactive environment. Cyclodextrins have been reviewed by Jozsef Szejtli in Chem. Rev. (1998), **98**, 1743-53.

25

30

Abbreviations

CD	cyclodextrin
DMSO	dimethylsulphoxide
2-HP-CD	2-hydroxypropyl- β -cyclodextrin
HTMPS	high throughput multiple parallel synthesis
HTS	high throughput screening
OC	octylcycloside
OTGP	octylthioglucopyranoside
PEG	polyethyleneglycol
SDS	sodium dodecyl sulphate

The invention will now be illustrated by the following non-limiting Examples in which:

- 5 **Figure 1** shows the percentage of compounds retaining their biological activity after different treatments compared with the initial number of biologically active compounds (actives) in DMSO-solution. The compounds were dissolved in DMSO, water or cyclodextrin (40 mM) in DMSO, and used either in liquid or after the liquid has evaporated (dry). Three different assay-methods were used: *Enzyme assay*: Enzyme activity was monitored in an aqueous
- 10 buffer system by absorbance changes. *Receptor assay*: binding of isotopically labelled ligand to membrane preparations in an aqueous buffer system was measured by scintillation. *Cellular assay*: A functional cell response was monitored after induction in aqueous medium by luminescence measurement.

- Figure 2** shows the percentage of compounds retaining their biological activity after different
- 15 treatments compared to the initial number of biologically active compounds (actives) in Cyclodextrin-DMSO-solution (40mM). The compounds were dissolved in Solutol™-DMSO (0.1 mM), Polyethyleneglycol-DMSO (20%), SDS-DMSO (20 mM), Octyl-Thioglucopyranoside-DMSO (20 mM) and Octylcycloside-DMSO (50 mM) and used either in liquid or after the liquid has evaporated (dry). Solutol™ is sold by BASF as nonionic
- 20 solubilizer in paste form for use in human and veterinary injections and is described in the BASF catalogue as "Solutol HS 15: macrogol-15 hydroxystearate produced by reacting 15 moles of ethyl oxide with 1 mole of 12-hydroxystearic acid". The same assays as in Example 1 were used.

Example 1

Compound accessibility after drying and aqueous dilution.

A selection of 80 compounds of known biological activity and poor aqueous solubility
5 were screened in 3 different biological systems (enzyme and receptor binding assays), in the presence and absence of cyclodextrin (40mM 2-HP-CD) in the organic solvent.

The enzyme assay was a peroxidase assay with a chromogenic substrate. The receptor
assay was a G-protein coupled receptor assay performed as SPA™ (Amersham, scintillation
proximity assay technology) with a membrane preparation linked to scintillant beads and a
10 radiolabelled ligand. The cellular assay was a cytokine stimulated monocyte cell-line
providing a measurable luminescent response.

The compounds were exposed to drying conditions and aqueous dilution (conditions
which can cause precipitation of the compounds), and then tested in the biological assays, in a
manner equivalent to the standard HTS process. The results are shown in Figure 1.

15 The findings are as follows:

Increased solubility in aqueous solutions, more compounds stay in solution without
precipitating, resulting in more active compounds identified.

Conserved biological activity after drying in the reaction vessel: compounds that have shown
activity on a certain target lose that activity if the compound dried out due to DMSO
20 evaporation prior to the biological assay. When CD is present those active compounds keep
their activity also after being dried.

Several effects were demonstrated:

- Cyclodextrin itself did not affect the normal functioning of the biological assays tested.
- 25 • In the absence of cyclodextrin the drying conditions of the compounds cause loss of all or most of the biological activities caused by the compounds
- In the presence of cyclodextrin all of the known biological activities of the compounds were retained after the drying treatments.

Example 2

30 HTS experiments with 1600 compounds

1600 different compounds screened in the presence and absence of cyclodextrin (2-HP-CD, 50 mM). These experiments provided further confirmation of the preliminary

observations, although this time with a larger number of compounds, not pre-selected for low solubility properties. The results were not as clear-cut as in the preliminary trials, but still very promising.

Firstly, the cyclodextrin did not adversely affect the biological assays, in common with the first trials. Further, it generally revealed more biological activity of the compounds than was seen without cyclodextrin after drying or aqueous dilution treatments, which could otherwise result in compound loss by precipitation.

Several effects were demonstrated:

Increased bioavailability of compounds for the target: Molecules that did not show activity in the absence of CD, can become active because the bioavailability is improved by CD, making for example lipophilic compounds soluble in aqueous solution.

Increased solubility in aqueous solutions, more compounds stay in solution without precipitating, thus resulting in more active compounds

Conserved biological activity if it is necessary to dilute compounds in aqueous solution prior to the assay: compounds that have shown activity on a certain target may lose that activity due to precipitation if the compound is diluted in aqueous solution prior to the assay. When CD is present those compounds mostly keep their activity because precipitation is prevented.

Comparative Example 1

20 Comparison of Cyclodextrin with other possible protective agents

The same experimental setup as in Example 1 was used to compare the performance of cyclodextrin with other potential protective agents. None of the other agents showed the advantageous properties (e.g. biologically inert, protective in dry conditions) as well as cyclodextrin; see Figure 2.

25 The conclusion was that CD was by a large margin the best protective agent tested.

Claims

- 1 A compound library wherein each compound within the library is stored in the presence of a cyclodextrin wherein the cyclodextrin concentration is 20-200mM.
- 2 A compound library according to claim 1 comprising at least 1000 compounds.
- 5 3 A compound library according to claim 1 comprising at least 10000 compounds.
- 4 A compound library according any preceding claim wherein the compounds are organic molecules of molecular weight of less than 2000 Daltons.
- 5 A compound library according to claim 4 wherein the compounds are organic molecules of molecular weight of less than 1000 Daltons.
- 10 6 A compound library according to any preceding claim wherein the cyclodextrin concentration is 30-150mM.
- 7 A compound library according to any preceding claim wherein the cyclodextrin concentration is 40-80mM.
- 8 A compound library according to any preceding claim wherein the cyclodextrin concentration is 45-60mM.
- 15 9 A compound library according to any preceding claim wherein the cyclodextrin concentration is 50mM.
- 10 A compound library according to any preceding claim wherein the cyclodextrin is 2-hydroxypropyl- β -cyclodextrin.
- 20 11 A compound library according to any preceding claim in wet form.
- 12 A method of preparing a compound library as defined in any of claims 1-11 which comprises the addition of a cyclodextrin to each compound within the library and storage of the compound library in wet form.
- 13 A method of screening a compound library as defined in any of claims 1-11 which
- 25 comprises assay of at least 100 compounds from the library.
- 14 A method according to claim 13 in which the assay is selected from the group consisting of enzyme assay, receptor assay and cellular assay.

ABSTRACT

CHEMICAL COMPOUNDS

The invention relates to cyclodextrin as a protective agent for compounds in compound libraries, particularly for use in screening the compound library for biological activity. A particular advantage is improved recovery of potential activity of compounds within the library when the compounds have dried on storage.

Figure 1

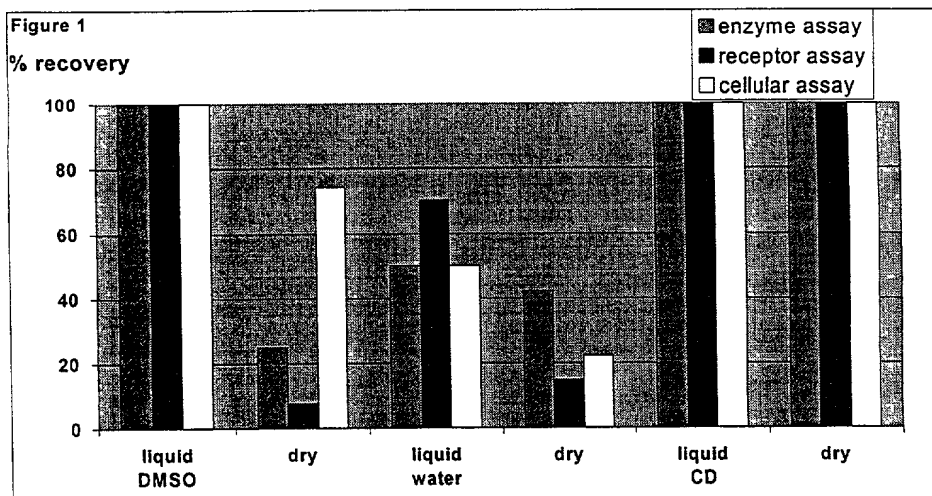
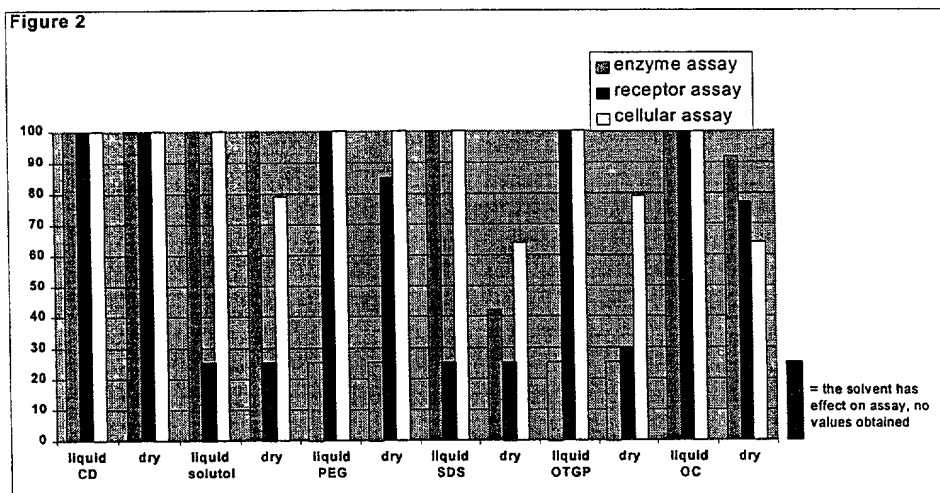
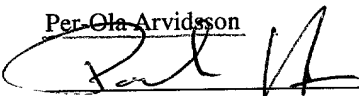


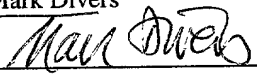
Figure 2

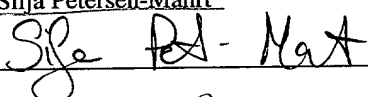


COMBINED DECLARATION AND POWER OF ATTORNEY CONTINUED

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

1-00
Full Name of Inventor: Per-Ola Arvidsson
Inventor's Signature:  Date: 17 Dec 2000
Residence Address: Hjärup, Sweden SEX
Stora Råby
Citizen of: Sweden
Post Office Address: AstraZeneca R&D Lund, S-221 87 Lund, Sweden

2-00
Full Name of Inventor: Mark Divers
Inventor's Signature:  Date: 22 November 2000
Residence Address: Malmö, Sweden SEX
Citizen of: United Kingdom
Post Office Address: AstraZeneca R&D Lund, S-221 87 Lund, Sweden

3-00
Full Name of Inventor: Silja Petersen-Mahrt
Inventor's Signature:  Date: 27. November 2000
Residence Address: Hjärup, Sweden SEX
Citizen of: Germany
Post Office Address: AstraZeneca R&D Lund, S-221 87 Lund, Sweden

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled CHEMICAL COMPOUNDS, the specification of which

- ☐ is attached hereto.
☐ was filed on as Application Serial No. and was amended on (if applicable).
☒ was described and claimed in PCT International Application No. PCT/SE00/01592 filed on 21 August 2000 and was amended under PCT Article 19 on (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

COUNTRY	APPLICATION NO.	FILING DATE	PRIORITY CLAIMED
<u>Sweden</u>	<u>9902988-6</u>	<u>24 August 1999</u>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

⑧ I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Janis K. Fraser, Reg. No. 34,819; William E. Booth, Reg. No. 28,933; John W. Freeman, Reg. No. 29,066; J. Peter Fasse, Reg. No. 32,983; Timothy A. French, Reg. No. 30,175; Eldora L. Ellison, Reg. No. 39,967; John J. Gagel, Reg. No. 33,499; John F. Hayden, Reg. No. 37,640.

Address all telephone calls to Janis K. Fraser, Esq. at telephone number 617/542-5070.

Address all correspondence to Janis K. Fraser, Esq., Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804.

I hereby authorize the attorneys and/or agents named above to accept and follow instructions from my representative, as to any actions to be taken in the Patent and Trademark Office regarding the above identified application without direct communication between the attorneys and me. In the event of a change in the person(s)

COMBINED DECLARATION AND POWER OF ATTORNEY CONTINUED

from whom instructions may be taken, I will notify the attorneys.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000
1001
1002
1003
1004
1005
1006
1007
1008
1009
1010
1011
1012
1013
1014
1015
1016
1017
1018
1019
1020
1021
1022
1023
1024
1025
1026
1027
1028
1029
1030
1031
1032
1033
1034
1035
1036
1037
1038
1039
1040
1041
1042
1043
1044
1045
1046
1047
1048
1049
1050
1051
1052
1053
1054
1055
1056
1057
1058
1059
1060
1061
1062
1063
1064
1065
1066
1067
1068
1069
1070
1071
1072
1073
1074
1075
1076
1077
1078
1079
1080
1081
1082
1083
1084
1085
1086
1087
1088
1089
1090
1091
1092
1093
1094
1095
1096
1097
1098
1099
1100
1101
1102
1103
1104
1105
1106
1107
1108
1109
1110
1111
1112
1113
1114
1115
1116
1117
1118
1119
1120
1121
1122
1123
1124
1125
1126
1127
1128
1129
1130
1131
1132
1133
1134
1135
1136
1137
1138
1139
1140
1141
1142
1143
1144
1145
1146
1147
1148
1149
1150
1151
1152
1153
1154
1155
1156
1157
1158
1159
1160
1161
1162
1163
1164
1165
1166
1167
1168
1169
1170
1171
1172
1173
1174
1175
1176
1177
1178
1179
1180
1181
1182
1183
1184
1185
1186
1187
1188
1189
1190
1191
1192
1193
1194
1195
1196
1197
1198
1199
1200
1201
1202
1203
1204
1205
1206
1207
1208
1209
1210
1211
1212
1213
1214
1215
1216
1217
1218
1219
1220
1221
1222
1223
1224
1225
1226
1227
1228
1229
1230
1231
1232
1233
1234
1235
1236
1237
1238
1239
1240
1241
1242
1243
1244
1245
1246
1247
1248
1249
1250
1251
1252
1253
1254
1255
1256
1257
1258
1259
1260
1261
1262
1263
1264
1265
1266
1267
1268
1269
1270
1271
1272
1273
1274
1275
1276
1277
1278
1279
1280
1281
1282
1283
1284
1285
1286
1287
1288
1289
1290
1291
1292
1293
1294
1295
1296
1297
1298
1299
1300
1301
1302
1303
1304
1305
1306
1307
1308
1309
1310
1311
1312
1313
1314
1315
1316
1317
1318
1319
1320
1321
1322
1323
1324
1325
1326
1327
1328
1329
1330
1331
1332
1333
1334
1335
1336
1337
1338
1339
1340
1341
1342
1343
1344
1345
1346
1347
1348
1349
1350
1351
1352
1353
1354
1355
1356
1357
1358
1359
1360
1361
1362
1363
1364
1365
1366
1367
1368
1369
1370
1371
1372
1373
1374
1375
1376
1377
1378
1379
1380
1381
1382
1383
1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414
1415
1416
1417
1418
1419
1420
1421
1422
1423
1424
1425
1426
1427
1428
1429
1430
1431
1432
1433
1434
1435
1436
1437
1438
1439
1440
1441
1442
1443
1444
1445
1446
1447
1448
1449
1450
1451
1452
1453
1454
1455
1456
1457
1458
1459
1460
1461
1462
1463
1464
1465
1466
1467
1468
1469
1470
1471
1472
1473
1474
1475
1476
1477
1478
1479
1480
1481
1482
1483
1484
1485
1486
1487
1488
1489
1490
1491
1492
1493
1494
1495
1496
1497
1498
1499
1500
1501
1502
1503
1504
1505
1506
1507
1508
1509
1510
1511
1512
1513
1514
1515
1516
1517
1518
1519
1520
1521
1522
1523
1524
1525
1526
1527
1528
1529
1530
1531
1532
1533
1534
1535
1536
1537
1538
1539
1540
1541
1542
1543
1544
1545
1546
1547
1548
1549
1550
1551
1552
1553
1554
1555
1556
1557
1558
1559
1560
1561
1562
1563
1564
1565
1566
1567
1568
1569
1570
1571
1572
1573
1574
1575
1576
1577
1578
1579
1580
1581
1582
1583
1584
1585
1586
1587
1588
1589
1590
1591
1592
1593
1594
1595
1596
1597
1598
1599
1600
1601
1602
1603
1604
1605
1606
1607
1608
1609
1610
1611
1612
1613
1614
1615
1616
1617
1618
1619
1620
1621
1622
1623
1624
1625
1626
1627
1628
1629
1630
1631
1632
1633
1634
1635
1636
1637
1638
1639
1640
1641
1642
1643
1644
1645
1646
1647
1648
1649
1650
1651
1652
1653
1654
1655
1656
1657
1658
1659
1660
1661
1662
1663
1664
1665
1666
1667
1668
1669
1670
1671
1672
1673
1674
1675
1676
1677
1678
1679
1680
1681
1682
1683
1684
1685
1686
1687
1688
1689
1690
1691
1692
1693
1694
1695
1696
1697
1698
1699
1700
1701
1702
1703
1704
1705
1706
1707
1708
1709
1710
1711
1712
1713
1714
1715
1716
1717
1718
1719
1720
1721
1722
1723
1724
1725
1726
1727
1728
1729
1730
1731
1732
1733
1734
1735
1736
1737
1738
1739
1740
1741
1742
1743
1744
1745
1746
1747
1748
1749
1750
1751
1752
1753
1754
1755
1756
1757
1758
1759
1760
1761
1762
1763
1764
1765
1766
1767
1768
1769
1770
1771
1772
1773
1774
1775
1776
1777
1778
1779
1780
1781
1782
1783
1784
1785
1786
1787
1788
1789
1790
1791
1792
1793
1794
1795
1796
1797
1798
1799
1800
1801
1802
1803
1804
1805
1806
1807
1808
1809
1810
1811
1812
1813
1814
1815
1816
1817
1818
1819
1820
1821
1822
1823
1824
1825
1826
1827
1828
1829
1830
1831
1832
1833
1834
1835
1836
1837
1838
1839
1840
1841
1842
1843
1844
1845
1846
1847
1848
1849
1850
1851
1852
1853
1854
1855
1856
1857
1858
1859
1860
1861
1862
1863
1864
1865
1866
1867
1868
1869
1870
1871
1872
1873
1874
1875
1876
1877
1878
1879
1880
1881
1882
1883
1884
1885
1886
1887
1888
1889
1890
1891
1892
1893
1894
1895
1896
1897
1898
1899
1900
1901
1902
1903
1904
1905
1906
1907
1908
1909
1910
1911
1912
1913
1914
1915
1916
1917
1918
1919
1920
1921
1922
1923
1924
1925
1926
1927
1928
1929
1930
1931
1932
1933
1934
1935
1936
1937
1938
1939
1940
1941
1942
1943
1944
1945
1946
1947
1948
1949
1950
1951
1952
1953
1954
1955
1956
1957
1958
1959
1960
1961
1962
1963
1964
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
2026
2027
2028
2029
2030
2031
2032
2033
2034
2035
2036
2037
2038
2039
2040
2041
2042
2043
2044
2045
2046
2047
2048
2049
2050
2051
2052
2053
2054
2055
2056
2057
2058
2059
2060
2061
2062
2063
2064
2065
2066
2067
2068
2069
2070
2071
2072
2073
2074
2075
2076
2077
2078
2079
2080
2081
2082
2083
2084
2085
2086
2087
2088
2089
2090
2091
2092
2093
2094
2095
2096
2097
2098
2099
2100
2101
2102
2103
2104
2105
2106
2107
2108
2109
2110
2111
2112
2113
2114
2115
2116
2117
2118
2119
2120
2121
2122
2123
2124
2125
2126
2127
2128
2129
2130
2131
2132
2133
2134
2135
2136
2137
2138
2139
2140
2141
2142
2143
2144
2145
2146
2147
2148
2149
2150
2151
2152
2153
2154
2155
2156
2157
2158
2159
2160
2161
2162
2163
2164
2165
2166
2167
2168
2169
2170
2171
2172
2173
2174
2175
2176
2177
2178
2179
2180
2181
2182
2183
2184
2185
2186
2187
2188
2189
2190
2191
2192
2193
2194
2195
2196
2197
2198
2199
2200
2201
2202
2203
2204
2205
2206
2207
2208
2209
2210
2211
2212
2213
2214
2215
2216
2217
2218
2219
2220
2221
2222
2223
2224
2225
2226
2227
2228
2